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10/536,569	05/02/2006	Ulrich Wiesner	3026-008	2178

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
10/14/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@AVHLAW.COM

Office Action Summary	Application No.	Applicant(s)	
	10/536,569	WIESNER ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/19/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,17,22,23,25,26 and 28-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,17,22,23,25,26 and 28-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-13, 15, 18-21, 24 and 27 have been cancelled as filed on 6/19/09.

Claims 40-44 have been added as filed on 6/19/09.

Claims 14, 16, 17, 22, 23, 25, 26 and 28-44 are currently pending.

Claims 14, 16, 17, 22, 23, 25, 26 and 28-44 are being examined in this application.

Priority

2. This application is filed under 35 U.S.C 371 of PCT/US03/37963 (filed on 11/26/2003), which claims priority as a CIP of US patent application 10/306,614 (filed on 11/26/2002).

Information Disclosure Statement

3. The IDS filed on 6/19/09 has been considered. See the attached PTO 1449 forms.

Oath/Declaration

4. Applicant's filing of a new Oath and Declaration (as filed on 6/19/09) is acknowledged.

Specification

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. MPEP 608.01.

Claim Objection(s) / Rejection(s) Withdrawn

6. In light of applicants' amendments to the claims and arguments, the following claim rejection(s) as set forth in the previous office action is(are) withdrawn:

A.) Claims **14, 16, 17, 22-28** and **30-32** are rejected under **35 U.S.C. 102(b)** as being anticipated by **Graf** et al (Langmuir. Vol.15: 6170-6180; 1999; cited in IDS).

B.) Claims **14, 16, 17, 22-32** and **34-38** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Graf** et al (Langmuir. Vol.15: 6170-6180; 1999; cited in IDS), in view of **Amiche** (US 6,132,773; 10/17/2000) and if necessary in view of **van Blaaderen** et al (Langmuir. Vol.8: 2921-2931; 1992; cited in IDS).

C.) Claims **14, 16, 17** and **22-38** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Graf** et al (Langmuir. Vol.15: 6170-6180; 1999; cited in IDS), **Amiche** (US 6,132,773; 10/17/2000) and **van Blaaderen** et al (Langmuir. Vol.8: 2921-2931; 1992; cited in IDS) as applied to claims 14, 16, 17, 22-32 and 34-38 above, and further in view of **Gu** et al. (PGPUB 20020048800; 4/25/2002).

D.) Claims **14, 16, 17** and **22-38** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Graf** et al (Langmuir. Vol.15: 6170-6180; 1999; cited in IDS), in view of **Amiche** (US 6,132,773; 10/17/2000), **van Blaaderen** et al (Langmuir. Vol.8: 2921-2931; 1992;

cited in IDS), and **Gu** et al. (PGPUB 20020048800; 4/25/2002), and if necessary in view **Weiss** et al (US 6,207,392; 3/27/2001; cited in IDS).

E.) Claims 14, 16, 17 and 22-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim Objection(s) / Rejection(s) Maintained

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

'614

8. Claims 14, 16, 22-24, 26, 28 and 31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 60, 62, 64

and 66 of copending Application No. 10/306,614 (PGPUB 20040101822). Although the conflicting claims are not identical, they are not patentably distinct from each other because invention of the '614 application reads on the instant claimed product.

The '614 application claims methods of using a fluorescent nanoparticle comprising a conjugated ligand, core-shell structure, as well as mercapto functional groups. (e.g. Claim 48), which the fluorescent nanoparticles read on the fluorescent nanoparticle of the instant claims.

The '614 application also claims various properties such as size, shell coverage, etc., of the fluorescent nanoparticles, which also read on the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants requested the ODP rejection be held in abeyance. Applicants have not provided any specific traversal over the above ODP rejection. Thus, the above rejection is maintained for the reasons of record.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Trau

11. Claims **14, 16, 17, 22, 23, 25, 26, 28-32** and **34-38** are rejected under **35 U.S.C. 102(e)** as being anticipated by **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01).

The instant claims recite "A fluorescent silica-based nanoparticle comprising a fluorescent organic dye covalently conjugated to an organo-silane compound, wherein the fluorescent silica-based nanoparticle has a diameter from about 20 nm to about 200 nm and is conjugated to a ligand."

Trau et al, throughout the publication, teach methods of making and using fluorescent nanoparticles that are silica core-shell structure (e.g. Abstract).

For **claim 14**: The reference teaches making silica nanoparticles comprising interior and exterior surfaces (or core-shell structure) (e.g. [0085]+; Claim 1). The reference also teaches the fluorescent dyes are linked to the interior (or core) through organo-silane groups such as using APS (e.g. Abstract; claims; [0012]; [0033]; [0180]). The reference also teaches attaching various molecules (such as nucleic acids and polypeptides) to the silica particles (e.g. claims; [0019]; [0025]; [0051]). The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]). The reference also teaches the silica particles can have various diameters such as 80nm, 100nm, etc. (e.g. [0088]; [0019]).

For **claim 16**: The reference teaches nanoparticles with various diameter sizes such 80nm or smaller (e.g. e.g. [0088]; [0019]).

For **claim 17**: The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]).

For **claim 22**: The reference also teaches the interior of the organosilica particles comprise mercapto or thiol functional groups, and fluorescent dyes are linked to the interior (or core) through the thiol groups (e.g. Abstract; claims; [0033]; [0180]).

For **claim 23**: The reference teaches silica exterior/shell (e.g. [0085]+; Claim 1; Abstract), which reads on the silica shell.

For **claim 25**: Although the cited references do not explicit teach the specific fluorescent quantum yield as recited in the claim, the fluorescent quantum yield is an inherent property of the nanoparticles. As discussed supra, the nanoparticles of the references' teachings have been

demonstrated to be structurally the same as the instant claimed nanoparticles, the nanoparticles of the references would inherent possess the same property.

For **claim 26**: The reference teaches making and using silica nanoparticles comprising interior and exterior surfaces (or core-shell structure) (e.g. [0085]+; Claim 1). The reference also teaches the interior of the organosilica particles comprise mercapto or thiol functional groups, and fluorescent dyes are linked to the interior (or core) through the thiol groups (e.g. Abstract; claims; [0033]; [0180]). The reference also teaches attaching various molecules (such as nucleic acids and polypeptides) to the silica particles (e.g. claims; [0019]; [0025]; [0051]). The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]). The reference also teaches the silica particles can have various diameters such as 80nm, 100nm, etc. (e.g. [0088]; [0019]). The reference teaches silica exterior/shell (e.g. [0085]+; Claim 1; Abstract).

For **claim 28**: The reference teaches nanoparticles with various diameter sizes such 80nm or smaller (e.g. e.g. [0088]; [0019]).

For **claim 29**: The reference teaches core nanoparticle sizes such as 2nm or above (e.g. [0019]).

For **claim 30**: Although the cited references do not explicit teach the specific fluorescent quantum yield as recited in the claim, the fluorescent quantum yield is an inherent property of the nanoparticles. As discussed supra, the nanoparticles of the references' teachings have been demonstrated to be structurally the same as the instant claimed nanoparticles, the nanoparticles of the references would inherent possess the same property.

For **claim 31**: The reference teaches linking various organic fluorescent compound (e.g. Figures; [0012]; [0019]).

For **claim 32**: The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]).

For **claim 34**: The reference teaches nanoparticles with various diameter sizes such 80nm or smaller (e.g. e.g. [0088]; [0019]), which the 80nm diameter particle inherently possess a core of with a size of less than 300 nm. The reference teaches core nanoparticle sizes such as 2nm or above (e.g. [0019]). The reference also teaches the fluorescent dyes are linked to the interior (or core) through organo-silane groups such as using APS (e.g. Abstract; claims; [0012]; [0033]; [0180]). The reference also teaches attaching various molecules (such as nucleic acids and polypeptides) to the silica particles (e.g. claims; [0019]; [0025]; [0051]). The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]). The reference teaches silica exterior/shell (e.g. [0085]+; Claim 1; Abstract), which reads on the silica shell.

For **claim 35**: The reference teaches nanoparticles with various diameter sizes such 80nm or smaller (e.g. e.g. [0088]; [0019]).

For **claim 36:** The reference also teaches the fluorescent dyes are covalently linked to the interior (or core) through organo-silane groups such as using APS (e.g. Abstract; claims; [0012]; [0033]; [0180]).

For **claim 37**: The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]).

For **claim 38**: The reference also teaches the interior of the organosilica particles comprise mercapto or thiol functional groups, and fluorescent dyes are linked to the interior (or core) through the thiol groups (e.g. Abstract; claims; [0033]; [0180]).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Trau and van Blaaderen

14. Claims **14, 16, 17, 22, 23, 25, 26, 28-32** and **34-44** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01) and in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234; 1994).

Trau et al, throughout the publication throughout the publication, teach methods of making and using fluorescent nanoparticles that are silica core-shell structure (e.g. Abstract), as

discussed supra. The rejection over Trau under section 102(e) above is hereby incorporated by reference in its entirety.

Trau does not explicit teach the range of nanoparticle sizes or core sizes as recited in claims 39, 40, etc..

However, Trau et al., throughout the reference teaches silica nanoparticles with various sizes include dye labeled colloidal nanoparticles with sizes ranging from 2nm to 100nm (e.g. [0019]). For the instant claims 41-44, the instant specification does not specifically define the specific structure of a "silica core", which can be broadly and reasonably interpreted to be any interior portion of the silica particle. The silica nanoparticle of the Trau reference inherently teaches the core sizes as recited in the said claims 41-44. For example, the interior center portion with a 2.2 nm radius is inherently possessed by each of the nanoparticles of the Trau reference.

In addition, **van Blaanderen** et al., throughout the publication, teach making silica spheres that are colloidal nanoparticles having sizes such as 30nm in diameter (e.g. Abstract). The reference also teaches silica particles having diameter as small as approximately 18nm in diameter depending on the method of preparation (e.g. pp.95+; Table II). The reference also teaches the size of the silica particle depends on the method of preparation and various with different solvents (e.g. p.87).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate silica nanoparticles labeled with fluorescent dye (and/or ligands) having various desired sizes such as less than 70nm.

A person of ordinary skill in the art would have been motivated at the time of the invention to make silica based nanoparticles with various diameter sizes including 18nm, 30nm,

etc., because van Blaaderen and Trau teach generating silica core-shell type of particles with various diameters are routine and known in the art depending on the application. In addition, because both the cited references teach making various silica nanoparticles (labeled or otherwise) with various particle diameters, it would have been obvious to one skilled in the art to substitute one size for the other to achieve the predictable result of generating fluorescence silica nanoparticles with desired sizes. It would have been obvious to one of ordinary skill in the art to apply the standard technique of generating a silica nanoparticle with desired size, as taught by both van Blaaderen and Trau, to improve the nanoparticles for the predicable result of enabling standard silica nanoparticles having fluorescent labels.

> In addition, "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference isclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)." (MPEP 2144.05)

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the techniques for generating the silica based nanoparticles with various functional groups for attaching fluorescent dyes and ligands, and the techniques for generating silica particles with various sizes are known and routine in the art as demonstrated by the cited references.

Trau and Others

15. Claims **14, 16, 17, 22, 23, 25, 26** and **28-44** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01) and in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234; 1994) as applied to claims 14, 16, 17, 22, 23, 25, 26, 28-32 and 34-44, and further in view of **Gu** et al. (PGPUB 20020048800; 4/25/2002; cited previously).

The combination of the Trau and van Blaaderen references teach nanoparticles with attached fluorescent labels, as discussed supra. The teaching of the combination of the said references under section 103(a) above is hereby incorporated by reference in its entirety.

The combination of said references (Trau and van Blaaderen) does not explicit teach the mercapto group is bonded to a maleimide as recited in **clm 33**.

However, **Gu** et al, throughout the patent teaches various methods/reagents for fluorescently labeling biological molecules (e.g. p.25). The reference teaches "a wide variety of amine-reactive and thiol-reactive fluorophore derivatives" can react with various groups including thiol groups (or mercapto groups) (e.g. [0347]). The reference also teaches various thiol-reactive fluorophores including "Alexa Fluor 488" are commercially available (e.g. [0348]+), which the "Alexa Fluor 488" inherently has "Maleimide" functional group fro reaction with the "thiol-reactive probes", as evidenced by the "Material Safety Data Sheet" and "Manual for Thiol-Reactive Probes" from Invitrogen (Downloaded from Invitrogen.com; Downloaded on 12/10/08).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate silica based "core-shell" structured nanoparticles with attached label through a mercapto-maleimide linkage especially when using a maleimide functional group containing fluorescent dye.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a maleimide functional containing dye to label nanoparticles, because Gu et al teach the convenience of using commercially available fluorescent dyes. In addition, it would have been obvious to a person of ordinary skill in the art to try the maleimide group containing fluorescent dye to label the nanoparticle of Trau through the mercapto (or thiol) functional group, to improve the labeling efficiency, as a person with ordinary skill has good reason to pursue the know options (such as either using amine-reactive or thiol-reactive labeling) within his or her technical grasp.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the techniques for attaching various fluorescent molecules through various reactive groups (such as thiol reactive) are known and routine in the art as demonstrated by the cited references.

Van Blaaderen 92 and Others

16. Claims **14, 16, 17, 22, 23, 25, 26** and **28-44** are rejected under **35 U.S.C. 102(e)** as being 35 U.S.C. 103(a) as being unpatentable over **van Blaaderen** et al. (Langmuir. Vol.8: 2921-2931; 1992; cited in IDS; referred to as van Blaaderen (92)), in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234; 1994;

referred to as van Blaaderen (94)), **Gu** et al. (PGPUB 20020048800; 4/25/2002; cited previously) and **Melde** et al. (Chem. Mater. Vol.11: 3302-3308; 1999).

Van Blaaderen et al, throughout the publication, teach methods of making and using fluorescent nanoparticles that are silica core-shell structure (e.g. Abstract).

For **claims 14, 17, 23, 26, 32, 34, 37, 39**, etc.: The reference teaches making silica core shell structure having fluorescent dyes (e.g. Abstract; Figure). The reference also teaches the fluorescent dyes are linked to the the core through organo-silane groups such as using APS (e.g. Figures; pp.2923+). The reference also teaches the silica particles can have various diameters such as 80nm, 100nm, etc. (e.g. Table 1). The instant specification does not specifically define the term "ligand" to comprise a particular structure. The dictionary defines the term "ligand" as "a group, ion, or molecule coordinated to a central atom or molecule in a complex" (see Definition for "Ligand" downloaded from Merriam-Webster Online Dictionary; downloaded on 12/10/08; cited previously). Thus, the term "ligand" broadly encompasses the various chemical groups. The reference teaches the silica shell of the nanoparticles are formed with chemical groups, which any of the chemical groups on the shell read on a ligand.

For **claims 25** and **30**: Although the cited references do not explicit teach the specific fluorescent quantum yield as recited in the claim, the fluorescent quantum yield is an inherent property of the nanoparticles. As discussed supra, the nanoparticles of the references' teachings have been demonstrated to be structurally the same as the instant claimed nanoparticles, the nanoparticles of the references would inherent possess the same property.

For **claims 31, 36**: The reference teaches covalently linking various organic fluorescent compounds (e.g. Figures).

For **claim 37**: The reference also teaches linker functional groups on the surface of the particles for linking other molecules such as DNA or proteins (e.g. [0033]; [0051]; [0166]).

For **claim 38**: The reference also teaches the interior of the organosilica particles comprise mercapto or thiol functional groups, and fluorescent dyes are linked to the interior (or core) through the thiol groups (e.g. Abstract; claims; [0033]; [0180]).

For the instant claims 41-44, the instant specification does not specifically define the specific structure of a "silica core", which can be broadly and reasonably interpreted to be any interior portion of the silica particle. The silica nanoparticle of the van Blaaderen (92) reference inherently teaches the core sizes as recited in the said claims 41-44. For example, the interior center portion with a 2.2 nm radius is inherently possessed by each of the nanoparticles of the van Blaaderen (92) reference.

Van Blaaderen (92) et al., do not explicitly teach the silica core comprising a mercapto group as well as the maleimide reactant as recited in claim 22, 26, 33, 38, etc. The reference also does not explicitly teach the various particle sizes as recited in claims 14, 16, 28, 29, 34, 35, etc.

However, **van Blaanderen** (94) et al., throughout the publication, teach making silica spheres that are colloidal nanoparticles having sizes such as 30nm in diameter (e.g. Abstract). The reference also teaches silica particles having diameter as small as approximately 18nm in diameter depending on the method of preparation (e.g. pp.95+; Table II). The reference also teaches the size of the silica particle depends on the method of preparation and various with different solvents (e.g. p.87).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate silica nanoparticles labeled with fluorescent dye (and/or ligands) having various desired sizes such as less than 70nm.

A person of ordinary skill in the art would have been motivated at the time of the invention to make silica based nanoparticles with various diameter sizes including 18nm, 30nm, etc., because both of the van Blaaderen teach generating silica core-shell type of particles with various diameters are routine and known in the art depending on the application. In addition, because both the cited references teach making various silica nanoparticles (labeled or otherwise) with various particle diameters, it would have been obvious to one skilled in the art to substitute one size for the other to achieve the predictable result of generating fluorescence silica nanoparticles with desired sizes. It would have been obvious to one of ordinary skill in the art to apply the standard technique of generating a silica nanoparticle with desired size, as taught by both van Blaaderen et al, to improve the nanoparticles for the predicable result of enabling standard silica nanoparticles having fluorescent labels.

> In addition, "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference isclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)." (MPEP 2144.05)

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the techniques for generating the silica based nanoparticles with various functional groups for attaching fluorescent dyes and ligands, and the

techniques for generating silica particles with various sizes are known and routine in the art as demonstrated by the cited references.

In additiona, **Melda**, throughout the publication, teaches silica nanoparticles having various functional groups such as a thiol functional group (e.g. p.3302; left. Col.).

Gu et al, throughout the patent teaches various methods/reagents for fluorescently labeling biological molecules (e.g. p.25). The reference teaches "a wide variety of amine-reactive and thiol-reactive fluorophore derivatives" can react with various groups including thiol groups (or mercapto groups) (e.g. [0347]). The reference also teaches various thiol-reactive fluorophores including "Alexa Fluor 488" are commercially available (e.g. [0348]+), which the "Alexa Fluor 488" inherently has "Maleimide" functional group fro reaction with the "thiol-reactive probes", as evidenced by the "Material Safety Data Sheet" and "Manual for Thiol-Reactive Probes" from Invitrogen (Downloaded from Invitrogen.com; Downloaded on 12/10/08; cited previously).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate silica based "core-shell" structured nanoparticles with attached label through a mercapto-maleimide linkage especially when using a maleimide functional group containing fluorescent dye, as well as to use silica nanoparticles having a mercapto group for conjugating a fluorescent dye in the silica core.

A person of ordinary skill in the art would have been motivated at the time of the invention to include mercapto functional groups in the silica particles for attaching various molecules such as fluorescent dye molecules, because Melde teaches it is routine and known in the art to functionalize silica particles with various chemical functional groups. In addition, because the cited references teach silica particles having various functional groups for attaching

ligands, dye labels, etc., for various assays, it would have been obvious to one skilled in the art to substitute one type label attaching chemistry for the other (depending on the chemical groups of the fluorescent dye) to achieve the predictable result of generating a labeled silica particle.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a maleimide functional containing dye to label nanoparticles, because Gu et al teach the convenience of using commercially available fluorescent dyes. In addition, it would have been obvious to a person of ordinary skill in the art to try the maleimide group containing fluorescent dye to label the nanoparticle through the mercapto (or thiol) functional group, to improve the labeling efficiency, as a person with ordinary skill has good reason to pursue the know options (such as either using amine-reactive or thiol-reactive labeling) within his or her technical grasp.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the techniques for attaching various fluorescent molecules through various reactive groups (such as thiol reactive) are known and routine in the art as demonstrated by the cited references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Primary Examiner, Art Unit 1639
10/8/09